change of ±16·5% of administered dose in a given individual reported by Tellez *et al* for ^{45}Ca absorption measured by a complex double isotope deconvolution technique.[8] It was hoped that a measurement of urine strontium excretion might also be a useful predictor of calcium absorption but the small percentage excreted over the five hours of the test made this an unreliable index.

The results obtained in the two patient groups confirm the utility of the strontium absorption test in clinical practice. Increased calcium absorption has been reported in some patients with primary hyperparathyroidism and this is confirmed here.[12] On the other hand, reduced absorption of calcium is known to occur in gluten induced enteropathy.[13] This has been attributed variously to a mucosal defect, complexing of calcium by unabsorbed fat, and vitamin D deficiency.[14] Our finding of strontium malabsorption in 10 out of 19 treated patients indicates a persisting abnormality despite clinical remission. The nature of this abnormality is currently being investigated.

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Gall stones in sickle cell disease in the United Kingdom

L R BOND, S R HATTY, M E C HORN, M DICK, H B MEIRE, A J BELLINGHAM

Abstract

The prevalence of gall stones was studied prospectively by abdominal ultrasound examination in 131 patients with sickle cell disease aged 10-65 years. Of 95 patients with homozygous sickle cell disease, 55 (58%) had gall stones or had had a cholecystectomy. Gall stones were present in four out of 24 (17%) patients with haemoglobin S+C disease and two out of 12 (17%) with haemoglobin Sβ thalassaemia. The presence of gall stones was not related to sex, geographical origin, or haematological variables and was not associated with abnormal results of liver function tests. Symptoms typical of biliary colic were reported by 32 out of 47 adult patients with gall stones, and cholecystitis or cholestasis was diagnosed in 18. Cholecystectomy was performed in 29 patients with good relief of symptoms in most cases. Postoperative complications were common, occurring in 10 of the 28 patients who could be evaluated, but not generally serious; they were considerably lessened by a preoperative exchange transfusion that reduced the haemoglobin S concentration to below 40%.

It is suggested that all patients with sickle cell disease should be screened routinely for gall stones and that elective cholecystectomy should be performed in those with symptoms or complications.

King's College Hospital, London SE5 9RS
L R BOND, BSC, MRCP, registrar, department of haematology
S R HATTY, MB, MRCP, registrar, department of haematology
M E C HORN, MB, DCH, research fellow, department of child health
M DICK, DCH, MRCP, research fellow, department of child health
H B MEIRE, MB, FRCR, consultant radiologist
A J BELLINGHAM, MB, FRCP, professor of haematology

Correspondence to: Dr L R Bond, Department of Haematology, St George's Hospital Medical School, London SW17 0RE.

Introduction

Gall stones are common in sickle cell anaemia owing to chronic haemolysis, but the importance of this complication has not been established. In the first two reports of sickle cell disease in 1910-11 both patients had recurrent "bilious" attacks, and one had a cholecystectomy.[1 2] The prevalence of gall stones reported in homozygous sickle cell disease (Hb SS) has varied widely, being from 34% to 70% in the United States,[3-5] 29% in Jamaica,[6] from 4% to 25% in Africa,[7 8] and 8% in Saudi Arabia.[9] This variability may reflect differences in the patients studied, age, and the sensitivity of diagnostic methods (plain radiography or oral cholecystography). Recently, ultrasonography has become a reliable non-invasive method for investigating the biliary tract. Prospective studies restricted to children have shown that the prevalence of gall stones is from 17% to 29% and increases with age,[10-13] but studies in adults are lacking.

Symptomatic biliary tract disease is difficult to diagnose in a patient with sickle cell disease who has acute abdominal pain, fever, and jaundice because such symptoms can occur in a vaso-occlusive crisis; in one study five out of seven patients who had emergency laparotomy for presumed acute cholecystitis had a normal gall bladder.[4] Equally, however, a diagnosis of "abdominal crisis" or "hepatic crisis" can mask attacks of biliary colic or cholestasis.[3 4 14 15] In the management of established gall bladder disease some workers have reported little relief of symptoms after cholecystectomy[3 4] but others have reported better results and suggested that surgery should be done in all cases.[5 11 14 16] Most authors have emphasised the increased surgical risks in these patients.

Sickle cell disease is now widespread in England and Wales,[17] but there have been no studies of gall bladder disease in British patients. We report a prospective study of patients aged 10-65 years attending the sickle cell clinics at this hospital, who were assessed by ultrasound examinations. We also review the results of cholecystectomy.

Patients and methods

All patients aged 10 years or more attending sickle cell clinics from March to December 1985 were asked to attend for an abdominal ultrasound examination unless they had had a cholecystectomy. For adult patients a standard questionnaire was used to elicit relevant symptoms and the clinical notes were reviewed for evidence of previous symptoms, admissions for abdominal crises, and possible biliary complications. Results of the following investigations were recorded: haemoglobin electrophoresis, steady state haemoglobin concentration, reticulocyte count, fetal haemoglobin (Hb F) concentration, and serial liver function tests. The patients who had had a cholecystectomy were asked about recurrent symptoms or complications in the same questionnaire, and their notes were reviewed.

All scans were performed with a real time mechanical sector scanner with a transducer frequency of 3·5 MHz for adults and 5 MHz for children. All patients were asked to fast for eight hours before the examination. Calculi were diagnosed if highly reflective structures, with or without acoustic shadowing, were detected within the lumen of the gall bladder.

Results of liver function tests (activities of alkaline phosphatase, aspartate transaminase, and γ-glutamyltransferase) were considered to be abnormal if one or more activities were greater than 1·5 times the upper limit of normal on two or more occasions.

Abdominal pain typical of biliary colic was defined as right hypochondrial (right upper quadrant) or epigastric pain of a steady, unremitting nature lasting more than one hour.[18] Any other abdominal pain was described as atypical.

Indigestion was defined as fat intolerance, abdominal pain or discomfort related to food, nausea or vomiting, fullness, belching, or water brash.[18]

Cholecystitis was defined as "biliary" pain and tenderness in the right upper quadrant lasting more than 72 hours with associated fever.

Cholestasis was defined as episodic jaundice with or without abdominal pain, dark urine, or pale stools, supported by raised liver enzyme activities.

Statistics—Haematological variables were compared with the unpaired *t* test with log transformation of serum bilirubin concentrations. Other observations were compared with the χ^2 test or Fisher's exact test for small samples. Data on the prevalence of gall stones are presented as survival curves with survival defined as the age up to which patients remained free of gall stones. Curves were compared with the log rank test.[19]

Results

PREVALENCE OF GALL STONES AND RESULTS OF TESTS

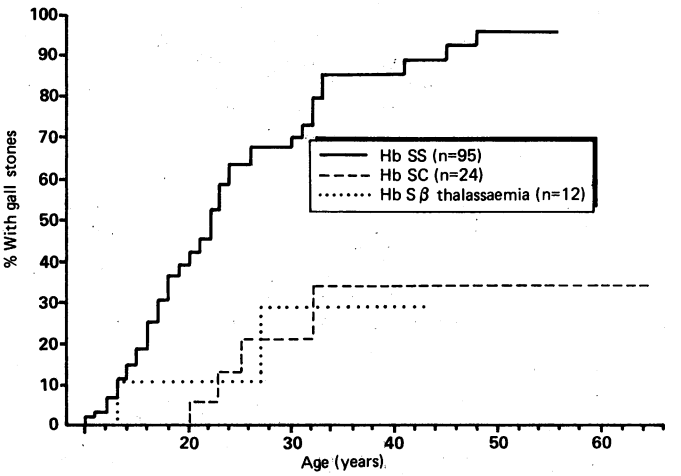
A total of 131 patients were studied out of 157 eligible patients (table I).

TABLE I—*Prevalence of gall stones in 131 patients with sickle cell disease according to age*

Age (years)	No of patients	No with gall stones	No with previous cholecystectomy	Prevalence (%) of gall stones and cholecystectomy
		Hb SS		
10-15	25	8	1	36
16-20	26	7	9	62
21-25	23	10	5	65
26-30	9	3	2	56
Over 30	12	8	2	83
Total	95	36	19	58
		Hb SC		
10-20	9	1		11
21-30	8	1	1	25
Over 30	7	1		14
Total	24	3	1	17
		Hb S β thalassaemia		
10-30	10	1	1	20
Over 30	2			
Total	12	1	1	17

Two examinations were technically unsatisfactory, and 24 patients failed to attend for ultrasound examination.

Of the 95 patients with Hb SS, 55 (58%) had gall stones or had had a cholecystectomy (table I). The prevalence increased to an expected 85% by the age of 33 (figure, 95% confidence interval 74% to 96%). Analysis adjusted for age showed no difference in prevalence according to sex ($p>0·30$) or between those of African and those of Caribbean origin ($p\geq0·80$).



Prevalence of gall stones in patients with sickle cell disease, showing age at first diagnosis or most recent negative ultrasound examination. Log rank test of Hb SS *v* Hb SC, $p<0·001$.

Gall stones were found in four of the 24 (17%) patients with haemoglobin S+C disease (Hb SC); two of the six (33%) with haemoglobin S β° thalassaemia (Hb S β° thalassaemia) (Hb A undetectable); and none of the six with haemoglobin S β⁺ thalassaemia (Hb S β⁺ thalassaemia) (HbA concentration 23-27%).

In the patients with Hb SS there were no significant differences in mean steady state haemoglobin, HbF and total bilirubin concentrations and reticulocyte count between those with and without gall stones (table II).

TABLE II—*Haematological variables in patients aged 10-25 with Hb SS*

	Patients with gall stones		Patients without gall stones		95% Confidence interval of difference between means	Significance (*t* test)
	No observed	Mean	No observed	Mean		
Hb (g/l)	43	81·1	30	80·2	−4·2 to 6·2	NS
Reticulocyte count (%)	30	8·13	30	9·22	−1·02 to 3·20	NS
Hb F (%)	40	5·58	33	5·70	−1·73 to 1·96	NS
Bilirubin (μmol/l)	28	50·17	15	37·22	0·966 to 1·88*	NS

* Ratio of differences with log transformed data.

Results of liver function tests other than bilirubin concentrations were persistently abnormal in 12 out of 95 patients (11 out of 62 with Hb SS) and raised during painful crises in another 13, but there was no association with the finding of gall stones.

SYMPTOMS AND COMPLICATIONS

Abdominal pain typical of biliary colic was reported by 32 of the 47 (68%) adult patients with gall stones. In 23 patients abdominal pain had resulted in hospital admission on at least one occasion. Only three of the 47 (6%) adults without gall stones described typical biliary pain within the past two years ($p<0·001$).

Indigestion typical of gall bladder disease was not strongly associated with gall stones (14 of those with gall stones and eight of those without, $p>0·10$). Intolerance to fatty food was described by six patients with no evidence of biliary disease. Complications were diagnosed in 18 (38%) of the adults with

gall stones. Ten patients developed acute cholecystitis, and symptoms of cholestatic jaundice were noted in 12. One patient developed acute pancreatitis.

CHOLECYSTECTOMY

Elective cholecystectomy was performed in 29 patients aged 10-32, including eight in whom gall stones were diagnosed during the period of the study. Preoperative management included exchange transfusion in all but one case, intravenous hydration, and postoperative oxygenation, mainly in the intensive therapy unit.[20] Pigment gall stones were found in all cases and pathological changes of chronic cholecystitis in all but two. Peroperative cholangiography was performed routinely and showed stones in the common bile duct in five patients. Four of these five patients had had recurrent attacks of jaundice, although one remained jaundiced postoperatively.

Postoperative complications, including acute sickle crisis (two patients) and chest infection (four patients), occurred in 10 of 28 (36%) patients who could be evaluated. When the preoperative Hb S (or Hb S+C) concentration was reduced by transfusion to below 40% infectious complications and sickle crises occurred in only three out of 19 patients, compared with five out of six in whom the Hb S concentration was above 40% (Fisher's exact test, $p=0{\cdot}01$). The most serious complication was a biliary stricture in a 10 year old boy, which later required bypass surgery.

Postoperative follow up of more than a year (range 18 months to 12 years) was possible in 14 patients. Eight remained free of pain, but four had abdominal pain during crises that was clearly different from their previous pain from gall stones. Two patients reported episodes typical of biliary colic, but both had normal findings on ultrasound examination and liver function testing, and one had a normal endoscopic retrograde cholangiogram.

Discussion

In this prospective study of a large population of British patients with sickle cell disease we found a high prevalence of gall stones, often associated with symptoms and related complications. In Hb SS gall stones occurred in half of our patients by the age of 22 and in 85% by the age of 33. The prevalence was much lower in Hb SC and Hb S β thalassaemia, as was found in two previous studies,[13 21] but was still two to three times that found in an older control population.[22]

In patients with Hb SS we found no evidence for a subgroup at higher risk of gall stones because of variables of haemolysis (concentrations of haemoglobin, Hb F, and bilirubin and reticulocyte count), sex, or geographical origin. A much lower prevalence of gall stones is reported in west African patients,[7 8] which might be explained by dietary differences, although the role of diet in the formation of pigment gall stones is unclear.

Two thirds of the patients with gall stones reported symptoms suggestive of biliary colic. Careful inquiry about the nature of the pain distinguished typical right upper quadrant and epigastric pain from the diffuse abdominal pain of sickle crises. This finding contrasts with the findings of some previous studies, but in those it was not always clear how symptoms were evaluated.[3 6 12] Some of our patients without gall stones, however, reported episodes of right hypochondrial pain, probably due to hepatic crises caused by sickling in the liver or intrahepatic cholestasis.[23] In most of our patients biliary colic and related complications were relieved by elective cholecystectomy. Any recurrent abdominal pain was mostly of a different nature and was easier to evaluate in the absence of the gall bladder. Indigestion and simple jaundice were poorly related to gall bladder disease. They did not generally improve after cholecystectomy and are thus poor indications for surgery unless cholestasis is shown.

Postoperative complications occurred in 36% of patients, but there was little serious morbidity and none of the patients died. We confirmed the value of preoperative exchange transfusion in patients with sickle cell disease as infectious and vaso-occlusive problems were clearly reduced in those with an Hb S concentration below 40% at operation. We therefore conclude that in an experienced centre elective cholecystectomy is a safe operation for patients with sickle cell disease who are appropriately prepared. It is particularly successful if symptoms are accurately evaluated and avoids the risks of emergency surgery in badly prepared patients.[4]

The best management of asymptomatic patients with gall stones is less clear. A limited follow up of patients with sickle cell disease suggested that half would develop symptoms or complications within three years,[4] but a larger longitudinal study is needed to establish the natural course of untreated gall stones. Meanwhile, we suggest that abdominal ultrasound examination and careful inquiry into symptoms should be routine in all adult patients with sickle cell disease. When gall stones are found together with typical abdominal symptoms or complications early elective cholecystectomy is indicated.

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